

EDITORIAL

Active cigarette smoking and asthma

N. C. Thomson, R. Chaudhuri and E. Livingston

Introduction

Active cigarette smoking is common in adult asthmatic patients and prevalence rates are similar to the general population. Current smoking rates among asthmatic patients range from 17% to 35% [1–7]. The highest rates are found in adults presenting to hospital emergency departments with acute asthma [3]. An additional number of adult asthmatics are former smokers with prevalence rates ranging from 22% to 43% [1, 2]. The large subgroup of adult asthmatics who are cigarette smokers has been excluded from many studies presumably because investigators were concerned that patients with smoking-related chronic obstructive pulmonary disease (COPD) might be included in the study population. Thus, there is relatively little published information on the influence of current cigarette smoking on asthma morbidity, therapeutic response to asthma medications and mechanisms of disease. In this edition of the journal, Sunyer et al. [8] examined the effects of asthma on peripheral cell blood counts among smokers and non-smokers and their results suggest that smoking modifies the immunological response in asthma. In this editorial we will assess this new data in the light of what is known about the clinical and immunological effects of active smoking in adults with asthma (Fig. 1).

Clinical effects of active smoking

The morbidity and mortality from asthma are increased in individuals who are cigarette smokers [1–5, 9–12]. Current asthmatic smokers have more severe asthma symptoms [1, 2] and worse indices of health status when compared with never smokers [4]. Cigarette smoking and asthma combine to accelerate the decline in lung function to a greater degree than either factor alone [7, 13]. Current smoking is associated with less appropriate management of asthma exacerbations, increased hospital-based care for asthma and more emergency department visits [3, 4, 10, 11]. The 6-year mortality rates are higher for smokers than non-smokers following a near-fatal asthma attack, with an age adjusted odd ratio of 3.6 [12], although there is conflicting evidence as to whether current smoking is a risk factor for near fatal asthma [5, 9].

Therapeutic response to corticosteroids

Corticosteroids are the most effective anti-inflammatory therapy for chronic asthma. Both national and international asthma guidelines emphasize the importance of the early introduction of inhaled corticosteroids as first-line therapy for

those with mild disease [14, 15]. The evidence for these recommendations is based on clinical trials that have been undertaken largely in asthmatic patients who are never smokers or former smokers. Until recently there was little information about the effect of active smoking on corticosteroid therapy in asthma. Active cigarette smoking impairs the efficacy of short-term inhaled corticosteroid treatment in steroid-naïve asthmatic patients [16]. In this randomized placebo-controlled study, the effect of treatment with inhaled fluticasone propionate, 1000 µg daily, or placebo for 3 weeks was studied in steroid-naïve adult asthmatic patients. Non-smokers had a significant increase in mean morning peak expiratory flow (PEF), mean forced expiratory volume in 1 s (FEV₁) and geometric mean PC₂₀ to methacholine and a significant decrease in sputum eosinophils following fluticasone compared to placebo. No significant changes were observed in the smoking asthmatics for any of these parameters. This result confirmed an earlier uncontrolled study that reported a reduced response to inhaled corticosteroids in terms of airway function in asthmatic smokers compared to non-smokers [17]. It remains to be established whether inhaled corticosteroid therapy, when administered for a longer duration, has beneficial effects on clinical endpoints including exacerbation rates.

Active smoking also impairs the efficacy of short-term oral corticosteroid treatment in chronic stable asthma [18]. The effect of treatment with prednisolone 40 mg daily or placebo for 2 weeks was studied in a randomized controlled trial of asthmatic smokers, ex-smokers and never-smokers. All subjects had clinical asthma with evidence of reversibility in FEV₁ after nebulized salbutamol of 15% and a mean post-bronchodilator FEV₁% predicted >80%. There was a significant improvement following oral prednisolone compared to placebo in FEV₁, morning PEF and asthma control score in asthmatic never smokers but no change in asthmatic smokers.

Taken together the results of these studies suggest that asthmatic smokers are resistant to corticosteroids. The effect of smoking on asthma may be partially reversible, since former smokers show improvement in morning PEF values but not asthma symptom control scores following a short course of oral corticosteroid treatment [18]. Previous work on resistance to corticosteroids in asthmatic smokers recruited individuals with a smoking pack history of ≥10 years [16, 18, 19] and it is unclear whether the response to corticosteroids is also decreased when the smoking history is of a lower intensity. Further studies are also required to determine whether corticosteroid responsiveness is regained following smoking cessation, and if so, how quickly the restoration of corticosteroid sensitivity occurs.

These findings may have important clinical implications for asthmatics who smoke and reinforce the need for smoking

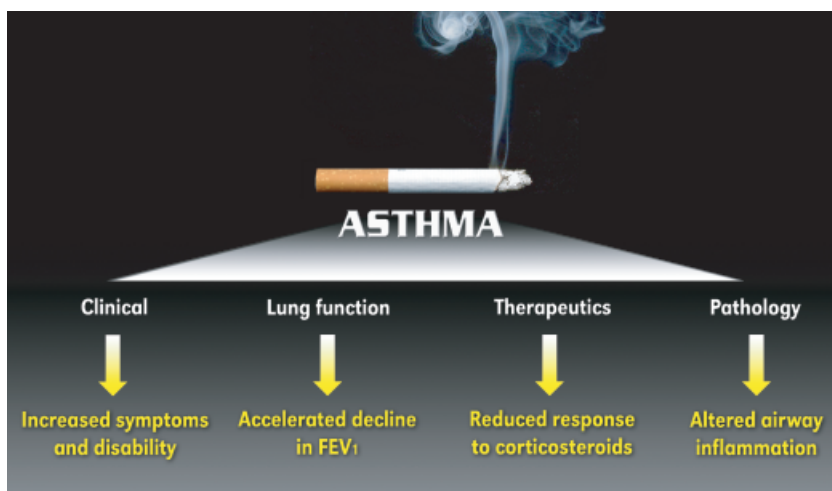


Fig. 1. Interaction of active cigarette smoking and asthma.

cessation in asthma, even in those with mild disease. Alternative or additional treatment to inhaled corticosteroids may be required for asthmatics who continue to smoke. Cigarette smoking causes a dose-related increase in urinary cysteinyl leukotriene E_4 production [20] and it would be of interest to examine the benefits on asthma control of leukotriene receptor antagonists in asthmatic smokers. Other therapies that would be worthy of study include long-acting β_2 receptor agonists [21] and phosphodiesterase-4 inhibitors [22].

Active smoking and inflammation in asthma

Circulating peripheral blood cells

In most but not all studies, current smoking is associated with increased circulating blood eosinophil counts in normal individuals [23–25] and asthma is also associated with raised circulating eosinophil counts [26]. In this edition of the journal, Sunyer et al. [8] report that circulating eosinophil counts are reduced in cigarette smokers with asthma compared with never-smokers with asthma, whereas the converse is true for non-asthmatic subjects. Circulating eosinophils, $CD4^+$ and $CD8^+$ T cell counts were measured in a cohort of HIV negative homosexual men ($n = 2194$), who were classified as having ($n = 197$) or not having asthma ($n = 1997$), based on a self-reported diagnosis of asthma. Data were collected semi-annually between 1987 and 1994 and the cohort remained HIV negative up to 2000. The odds ratio for circulating eosinophils being $\geq 4\%$ in asthma to non-asthma decreased from 2.7 (95% CI: 2.0, 3.6) to 1.5 (0.9, 2.3) in current smokers. Interestingly the odds ratio for ex-smokers was mid way between the figures for non-smokers and current smokers [2.1 (1.4, 3.1)]. In a small number of subjects ($n = 23$) who stopped smoking during the study, the proportion of circulating eosinophils increased in those with asthma, but fell in those who did not have asthma. Circulating peripheral blood T lymphocyte counts were similar in asthmatic smokers and non-smokers. There are several possible confounding factors that might influence the findings such as the study population of HIV-negative homosexual men, who have the potential to develop altered immune responses, and possible

uncertainties about the accuracy of the diagnosis of asthma and lack of information on drug treatment in the different asthma groups. The main findings are likely, however, to be valid in view of the consistent trend in circulating eosinophil counts between the different subgroups of asthmatic patients. The results point to an altered circulating inflammatory cell response in the asthmatic smokers and in particular suppression of the increased circulating blood eosinophil count that is associated with asthma.

The reason(s) for the reduced circulating eosinophil counts in asthmatic smokers compared to non-smokers is not clear. Cigarette smoke might suppress increased eosinophil production from the bone marrow in asthma. However, in animal experiments chronic cigarette exposure stimulates rather than suppresses the bone marrow to release more immature polymorphonuclear leukocytes into the circulation [27]. Other possible mechanisms include increased rate of removal of eosinophils from the circulation into inflamed airways in asthmatic smokers compared to non-smokers or perhaps more likely increased apoptosis of activated eosinophils by the actions of exogenous nitric oxide in cigarette smoke [28, 29]. Currently, there is no direct evidence for these postulated mechanisms in asthma. Sunyer et al. [8] have suggested that atopy might influence the interaction between smoking and asthma. In the general population, current cigarette smoking is positively associated with specific IgE antibodies to house dust mite [30] and to the risk of developing occupational asthma due to IgE-inducing agents [31], whereas bronchial hyper-reactivity is reduced in atopic non-asthmatic individuals who smoke compared to non-atopic normal subjects [32]. Thus, it is possible that the atopic status of an asthmatic might influence the immunological effects of active smoking. Whatever the mechanism for the interaction of cigarette smoking and peripheral blood eosinophil counts in asthma, the observations of Sunyer et al. [8] raises an important issue of whether airway inflammation in cigarette smokers who have asthma differs from that of asthmatic non-smokers.

Airway inflammation

Cigarette smoking induces predominately a non-eosinophilic inflammation within the airways of non-asthmatic smokers

without airflow obstruction compared to non-smokers [33–36]. In central airways T lymphocytes and macrophages are increased within the airway wall and neutrophils are increased within bronchial secretions [33]. Peripheral airways show an inflammatory cell wall infiltration with mononuclear cells and with macrophages in the respiratory bronchioles [33]. A raised airway eosinophil count is not a feature of most studies of asymptomatic smokers [33–34] although peripheral lung sections from smokers compared with non-smokers have been reported to show increased numbers of eosinophils infiltrating the submucosa [37]. Another study reported a slightly higher induced sputum eosinophil count from asymptomatic smokers compared to non-smoking controls [38], although the values found in the smokers were within the normal range and the finding has not been confirmed by others [19, 39]. Repeated exposure to cigarette smoke induces eosinophilic airway inflammation and bronchial hyper-reactivity in guinea pigs, possibly secondary to platelet-activating factor release [40]. Cigarette smoke might also have secondary immunomodulatory effects on eosinophils through nicotine-mediated inhibition of release of pro-inflammatory cytokines from macrophages [41, 42].

Cigarette smoking may modify airway inflammation associated with asthma, although to date, there is limited data on the influence of active smoking on airway pathology in asthma. Using induced sputum to assess airway inflammation, Chalmers et al. [19] found reduced eosinophil counts in samples from asthmatic smokers compared to non-smokers. In addition, smoking was associated with neutrophilic airway inflammation and a relationship was found between smoking history, levels of sputum IL-8 and lung function. Cigarette smoking reduces exhaled nitric oxide in mild steroid-naïve asthmatic smokers compared with asthmatic non-smokers [43] and it is thought that cigarette smoke may inhibit inducible nitric oxide synthase either due to the direct feedback effect of the high concentration of nitric oxide within the cigarette smoke itself [30] or by the carbon monoxide in the cigarette smoke interacting with haem proteins [44]. IL-18 is a cytokine that is known to have an important role in the development of a Th1 lymphocyte responses. As such, it may have a regulatory role in asthma by inhibiting Th2 lymphocyte responses. Smoking significantly reduces IL-18 level in induced sputum and this effect is more pronounced in asthmatics than in normal subjects [45]. These findings suggest that cigarette smoking may, in part, modify airway inflammation by potentially altering the balance of Th1/Th2 cytokine secretion. Other pathways that might contribute to airway inflammation in asthmatic smokers include increased airway epithelial permeability [46], neurogenic inflammation [47] and oxidative stress [48]. Finally, airway remodelling might be more severe in asthmatic smokers as the airway longitudinal elastic fibre network is increased in non-fatal asthmatic smokers compared with non-smokers [49].

The findings from these studies taken together point to a combination of both heightened and suppressed inflammatory responses in asthmatic smokers compared with asthmatic non-smokers. Further studies using both invasive and non-invasive techniques are required to assess cellular and structural changes in the airways of asthmatic smokers compared with asthmatic non-smokers and COPD. In

particular it will be important to establish whether the airway pathology of asthmatic smokers is predominantly that of asthmatic never-smokers, COPD or a combination of these two conditions.

Mechanisms of corticosteroid resistance in asthmatic smokers

Various different mechanisms have been implicated in corticosteroid resistance [50], but there have been no published studies in asthmatic smokers. Airway neutrophilia, which is found in asthmatics who have smoked for many years [19], is associated with a poor response to corticosteroids [51]. An increase in the number of glucocorticoid β receptors (GCR β) has been implicated as a mechanism for corticosteroid resistance [50, 52], and as neutrophils have a higher number of GCR β [53], this could account for the poor response to corticosteroids. Cigarette smokers have been shown to have an increase in the inflammatory cytokines IL-2 [54], IL-4 [55] and TNF- α [56], which have been implicated in corticosteroid resistance [57]. The precise mechanisms by which these cytokines might decrease corticosteroid responsiveness are unknown, but they have been reported to induce the expression of GCR β [53, 58]. NF- κ B has been associated with corticosteroid unresponsiveness in Crohn's disease [59], and it is possible that a similar mechanism exists in asthmatic smokers, as cigarette smoke contains bacterial lipopolysaccharide, an activator of NF- κ B [60]. Finally, glucocorticoids require histone deacetylase (HDAC) activity for maximal suppression of cytokine induction [61], but smokers have decreased HDAC activity and this may lead to an increase in inflammatory gene expression and reduced sensitivity to corticosteroids [62].

Conclusions

Active cigarette smoking is common in adult asthmatic patients and is associated with increased morbidity from asthma and impaired short-term therapeutic responses to corticosteroids. Cigarette smoking may modify the inflammation associated with asthma, but information is limited on the influence of active cigarette smoking on airway pathology in asthma and on the mechanisms of corticosteroid resistance in asthmatic smokers. The effect of smoking cessation on these processes is also not clear, but the findings to date help reinforce the importance of smoking cessation in asthma. It is likely that alternative or additional therapies to inhaled corticosteroids are needed for asthmatic patients who are unable to stop smoking.

References

- 1 Althuis MD, Sexton M, Prybylski D. Cigarette smoking and asthma symptom severity among adult asthmatics. *J Asthma* 1999; 36:257–64.
- 2 Siroux V, Pin I, Oryszczyn MP, Le Moual N, Kauffmann F. Relationships of active smoking to asthma and asthma severity in the EGEA study. *Eur Respir J* 2000; 15:470–7.

- 3 Silverman RA, Boudreaux ED, Woodruff PG, Clark S, Camargo CA Jr. Cigarette smoking among asthmatic adults presenting to 64 emergency departments. *Chest* 2003; 123:1472–9.
- 4 Sippel JM, Pedula KL, Vollmer WM et al. Associations of smoking with hospital-based care and quality of life in patients with obstructive airways disease. *Chest* 1999; 115:691–6.
- 5 Turner MO, Noertjojo K, Vedal S et al. Risk factors for near fatal asthma A case–control study in hospitalized patients with asthma. *Am J Respir Crit Care Med* 1998; 157:1804–9.
- 6 Walsh LJ, Wong CA, Cooper S, Guhan AR, Pringle M, Tattersfield AE. Morbidity from asthma in relation to regular treatment: a community based study. *Thorax* 1999; 54:296–300.
- 7 Apostol GG, Jacobs DR, Tsai AW et al. Early life factors contribute to the decrease in lung function between ages 18 and 40. *Am J Respir Crit Care Med* 2002; 166:166–72.
- 8 Sunyer J, Springer G, Jamieson B et al. The effects of asthma on cell components in peripheral blood among smokers and non-smokers. *Clin Exp Allergy* 2003; 33:1500–55.
- 9 LeSon S, Gershwin ME. Risk factors for asthmatic patients requiring intubation. III. Observations in young adults. *J Asthma* 1996; 33:27–35.
- 10 Marks GB, Burney PGJ, Premaratne UN et al. Asthma in Greenwich, UK: impact of the disease and current management practices. *Eur Respir J* 1997; 10:1224–9.
- 11 Cassino C, Ito K, Bader I et al. Cigarette smoking and ozone-associated emergency department use for asthma by adults in New York City. *Am J Respir Crit Care Med* 1999; 159:1773–9.
- 12 Marquette CH, Saulnier F, Leroy O et al. Long-term prognosis of near-fatal asthma. *Am Rev Respir Dis* 1992; 146:76–81.
- 13 Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998; 339:1194–1200.
- 14 Global initiative for asthma: global strategy for asthma management and prevention. NHLBI/WHO Report 95-3695, Bethesda, MD, 1995.
- 15 British Guideline on the Management of Asthma. *Thorax* 2003; 58 (Suppl. 1): i1–94.
- 16 Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax* 2002; 57:226–30.
- 17 Pedersen B, Dahl R, Karlstrom R, Peterson CG, Venge P. Eosinophil and neutrophil activity in asthma in a one-year trial with inhaled budesonide. The impact of smoking. *Am J Respir Crit Care Med* 1966; 153:1519–29.
- 18 Chaudhuri R, Livingston E, Thomson L et al. Effect of cigarette smoking on the therapeutic response to oral corticosteroids in chronic asthma. *Am J Respir Crit Care Med* 2003 (in press).
- 19 Chalmers GW, MacLeod KJ, Thomson LJ, Little SA, McSharry CP, Thomson NC. Smoking and airway inflammation in patients with mild asthma. *Chest* 2001; 120:1917–22.
- 20 Fauler J, Frölich JC. Cigarette smoking stimulates cysteinyl leukotriene production in man. *Eur J Clin Invest* 1997; 27:43–7.
- 21 Barnes PJ. Scientific rationale for inhaled combination therapy with long-acting β_2 -agonists and corticosteroids. *Eur Respir J* 2002; 19:182–91.
- 22 Johnson DC. A role for phosphodiesterase type-4 inhibitors in COPD. *Lancet* 2001; 358:256–7.
- 23 Halonnen M, Barbee R, Lebowitz MD, Burrows B. An epidemiological study of the interrelationship of total serum immunoglobulin E, allergy skin tests reactivity and eosinophilia. *J Allergy Clin Immunol* 1982; 69:221–8.
- 24 Taylor RG, Gross E, Holland F, Pride NB. Smoking, allergy and the differential white cell count. *Thorax* 1985; 40:17–22.
- 25 Jensen EJ, Pedersen B, Narvestadt E et al. Blood eosinophil and monocyte counts are related to smoking and lung function. *Respir Med* 1998; 92:63–9.
- 26 Ulrik CS. Peripheral eosinophil counts as a marker of disease activity in intrinsic and extrinsic asthma. *Clin Exp Allergy* 1995; 25:820–7.
- 27 Terashima T, Wiggs B, English D et al. The effect of cigarette smoking on the bone marrow. *Am J Respir Crit Care Med* 1997; 155:1021–6.
- 28 Zhang X, Moilanen E, Lahti A et al. Regulation of eosinophil apoptosis by nitric oxide: role of c-Jun-N-terminal kinase and signal transducer and activator of transcription 5. *J Allergy Clin Immunol* 2003; 112:93–101.
- 29 Assreuy J, Cunha F, Liew F et al. Feedback inhibition of nitric oxide synthase by nitric oxide. *Br J Clin Pharmacol* 1993; 108:833–7.
- 30 Jarvis D, Chinn S, Lucynska C, Burney P. The association of smoking with sensitization to common environmental allergens: results from the European Community Health Survey. *J Allergy Clin Immunol* 1999; 104:934–40.
- 31 Venables KM, Chan-Yeung M. Occupational asthma. *Lancet* 1997; 349:1465–9.
- 32 Sunyer J, Anto JM, the Spanish Group of the European Study of Asthma et al. Smoking and bronchial responsiveness in non-atopic and atopic young adults. *Thorax* 1997; 52:235–8.
- 33 Saetta M, Turato G, Maestrell P et al. Cellular and structural bases of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163:1304–9.
- 34 Jeffery PK. Structural and inflammatory changes in COPD: a comparison with asthma. *Thorax* 1998; 53:129–36.
- 35 Roth MD, Arora A, Kogevinas M et al. Airway inflammation in young marijuana and tobacco smokers. *Am J Respir Crit Care Med* 1998; 157:928–37.
- 36 Kuschner WG, D'Alessandro A, Wong H et al. Dose-dependent cigarette smoking-related inflammatory responses in health adults. *Eur Respir J* 1996; 9:1989–94.
- 37 Lams BEA, Sousa AR, Rees PJ et al. Immunopathology of the small-airway submucosa in smokers with and without chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 158:1518–23.
- 38 D'Ippolito R, Foresi A, Chetta A et al. Eosinophils in induced sputum from asymptomatic smokers with normal lung function. *Respir Med* 2001; 95:969–74.
- 39 Pizzichini E, Pizzichini MMM, Efthimiadis A et al. Indices of airway inflammation in induced sputum: reproducibility and validity of cell and fluid-phase measurements. *Am J Respir Crit Care Med* 1996; 154:308–17.
- 40 Matsumoto K, Aizawa H, Inoue H et al. Eosinophilic airway inflammation induced by repeated exposure to cigarette smoke. *Eur Respir J* 1998; 12:397–4.
- 41 Sopori ML, Kozak W. Immunomodulatory effects of cigarette smoke. *J Neuroimmunol* 1998; 83:148–56.
- 42 Wang H, Yu M, Oham M et al. Nicotinic acetylcholine receptor $\alpha 7$ subunit is an essential regulator of inflammation. *Nature* 2003; 421:348–88.
- 43 Verleden G, Dupont L, Verpeut A et al. The effect of cigarette smoke on exhaled nitric oxide in mild steroid-naive asthmatics. *Chest* 1999; 116:59–64.
- 44 White K, Marletta M. Nitric oxide synthase is a cytochrome P-450 type hemoprotein. *Biochemistry* 1992; 31:6627–31.
- 45 McKay A, Komai-Koma M, MacLeod KJ et al. Interleukin-18 levels in induced sputum are reduced in both asthmatic and normal smokers. *Thorax* 2001; 56 (Suppl. 3):iii81.
- 46 Rusznak C, Mills PR, Devalia JL et al. Effect of cigarette smoke on the permeability and IL-1 β and sICAM-1 release from cultured human epithelial cells of never-smokers, smokers and patients with chronic obstructive pulmonary disease. *Am J Respir Mol Biol* 2000; 23:530–6.

- 47 Kwong K, Wu Z-X, Kashon ML et al. Chronic smoking enhances tachykinin synthesis and airway responsiveness in guinea pigs. *Am J Respir Cell Mol Biol* 2001; 25:299–305.
- 48 MacNee W, Rahman I. Oxidants and antioxidants as therapeutic targets in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160:S58–65.
- 49 Carroll NG, Perry S, Karkhanis A et al. The airway longitudinal elastic fiber network and mucosal folding in patients with asthma. *Am J Respir Crit Care Med* 2000; 161:244–8.
- 50 Leung DYM, Bloom JW. Update on glucocorticoid action and resistance. *J Allergy Clin Immunol* 2003; 111:3–22.
- 51 Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw AJ, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. *Thorax* 2002; 57:875–9.
- 52 Sousa A, Lane S, Cidlowski J et al. Glucocorticoid resistance in asthma is associated with elevated *in vivo* expression of the glucocorticoid receptor β -isoform. *J Allergy Clin Immunol* 2000; 105:943–50.
- 53 Strickland I, Kisich K, Hauk P et al. High constitutive glucocorticoid receptor β in human neutrophils enables them to reduce their spontaneous rate of cell death in response to corticosteroids. *J Exp Med* 2001; 193:585–93.
- 54 Livingston E, Chaudhuri R, MacLeod K et al. Systemic corticosteroid sensitivity and lymphocyte IL-2 and IL-4 synthesis in cigarette smokers. *Am J Respir Crit Care Med* 2003; 167:A64.
- 55 Byron KA, Varigos GA, Wootton AM. IL-4 production is increased in cigarette smokers. *Clin Exp Immunol* 1994; 95:333–6.
- 56 Churg A, Dai J, Changshi X et al. Tumour necrosis factor- α is central to acute cigarette smoke-induced inflammation and connective tissue breakdown. *Am J Respir Crit Care Med* 2002; 166:849–54.
- 57 Kam J, Szefer S, Surs W et al. Combination IL-2 and IL-4 reduces glucocorticoid receptor-binding affinity and T cell response to glucocorticoids. *J Immunol* 1993; 151:3460–6.
- 58 Webster JC, Oakley RH, Jewell CM, Cidlowski JA. Pro-inflammatory cytokines regulate human glucocorticoid receptor gene expression and lead to the accumulation of the dominant negative β isoform: a mechanism for the generation of glucocorticoid resistance. *Proc Natl Acad Sci USA* 2001; 98:6865–70.
- 59 Bantel H, Schmitz ML, Raible A, Gregor M, Schulze-Osthoff K. Critical role of NF-kappaB and stress-activated protein kinases in steroid unresponsiveness. *FASEB J* 2002; 16:1832–4.
- 60 Wang JH, Manning BJ, Wu QD, Blankson S, Bouchier-Hayes D, Redmond HP. Endotoxin/lipopolysaccharide activates NF- κ B and enhances tumor cell adhesion and invasion through a β_1 integrin-dependent mechanism. *J Immunol* 2003; 170:795–804.
- 61 Ito K, Caramori G, Lim S et al. Expression and activity of histone deacetylases in human asthmatic airways. *Am J Respir Crit Care Med* 2002; 166:392–6.
- 62 Ito K, Lim J, Caramori G, Chung KF, Barnes P, Adcock IM. Cigarette smoking reduces histone deacetylase 2 expression, enhances cytokine expression, and inhibits glucocorticoid actions in alveolar macrophages. *FASEB J* 2001; 15:1110–2.

N. C. Thomson, R. Chaudhuri and E. Livingston
Department of Respiratory Medicine
Division of Immunology
Infection and Inflammation
Western Infirmary
University of Glasgow
Glasgow G11 6NT
UK
E-mail: n.c.thomson@clinmed.gla.ac.uk

